Published in final edited form as:

Org Lett. 2020 February 07; 22(3): 976–980. doi:10.1021/acs.orglett.9b04506.

Redox-Annulations of Cyclic Amines with *ortho*-Cyanomethylbenz-aldehydes

Anirudra Paul^{†,‡}, Hemant S. Chandak[‡], Longle Ma[‡], Daniel Seidel^{†,‡,*}

[†]Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611, United States

[‡]Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, United States

Abstract

Amines such as 1,2,3,4-tetrahydroisoquinoline undergo redox-neutral annulations with *ortho*-cyanomethylbenz-aldehydes. These amine α -C–H bond functionalization reactions are promoted by acetic acid. The resulting β -aminonitriles can be converted to the corresponding β -aminoalcohols in diastereoselective fashion.

Graphical Abstract

Redox-neutral methods for the α -C–H bond functionalization of amines provide an attractive platform for the rapid buildup of molecular complexity.^{1,2} This is particularly true when oxidative α -C–C or C–X bond formation is coupled to a reductive *N*-alkylation event, as is the case in a range of transformations involving secondary amines, an aldehyde or a ketone, and a (pro)-nucleophile.^{1m,1o} When the aldehyde and the (pro)-nucleophile are part of the same molecule, redox-annulations are possible, providing facile access to polycyclic ring systems. The earliest example of this type of transformation involves *ortho*-aminobenzaldehydes (Scheme 1, eq 1, X = NR) and was discovered serendipitously.³ In the presence of a carboxylic acid catalyst, other activated *ortho*-substituted benzaldehydes undergo related reactions, enabling C–O and C–S bond formation.⁴ To achieve α -C–C bond formation in redox-annulations with *ortho*-tolualdehyde derivatives, the presence of two electron-withdrawing groups on the *ortho*-methyl group was found to be necessary.⁵ Alternatively, activation of an *ortho*-methyl group has been achieved with heteroaryl substrates (Scheme 1, eq. 2)⁶ and highly electron-deficient *o*-tolualdehydes (Scheme 1, eq. 3).^{7–10} To further expand the scope of amine redox-annulations and to provide an attractive

*Corresponding Author: seidel@chem.ufl.edu.

Supporting Information

Experimental procedures and characterization data including the X-ray crystal structures of products **2a**, **2p** and **5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

pathway to new analogs of the tetrahydropyprotoberberine family of natural products,¹¹ we sought to develop more challenging transformations involving moderately activated *o*-tolualdehydes. Here we report the first redox-annulations of amines with *ortho*-tolualdehydes possessing a single activating group on the *ortho*-methyl group (Scheme 1, eq. 4).

Ortho-cyanomethylbenzaldehyde (**1a**) and 1,2,3,4-tetrahydroisoquinoline (THIQ) were selected as the model substrates in the initial evaluation of the proposed redox-annulation (Table 1). This transformation was found to occur under a range of conditions. The best reaction outcome in regard to overall efficiency was achieved with a small excess of THIQ (1.3 equiv) in the presence of acetic acid (20 equiv), using 1,2-dichloroethane as the solvent with heating under reflux for 4 h. Under these conditions, polycyclic β -aminonitrile was obtained in 92% yield as a separable 4:1 mixture of diastereomers (entry 5). An otherwise identical reaction performed in toluene, frequently the solvent of choice in related annulations, provided lower yields (entry 6). Interestingly, the addition of molecular sieves, while often beneficial, provided no improvements in this case (entry 8).

The scope of the redox-annulation of THIQ with various *ortho*-cyanomethylbenzaldehydes **1** is outlined in Scheme 2. Both electron-donating and electron-withdrawing substituents in different ring positions of the aromatic aldehyde were tolerated, furnishing products **2** in moderate to good yields. As summarized in Scheme 3, a range of THIQs with various ring substituents readily underwent redox-annulations with *ortho*-cyanomethylbenzaldehyde (**1a**) to provide products **2**. 1-Aryl-THIQs enabled the formation of tetrahydropyprotoberberine derivatives containing a tetrasubstituted stereogenic center. 1,2,3,4-Tetrahydro- β -carboline and 1-phenyl-1,2,3,4-tetrahydro- β -carboline were also identified as viable reaction partners (products **2n** and **2o**).

The use of relatively activated benzylic amines was found to be a requirement for achieving redox-annulations with *ortho*-cyanomethylbenzaldehydes **1**. For instance, amines such as pyrrolidine and piperidine failed to productively engage **1a**. As has been demonstrated by us and others, decarboxylative annulations of α -amino acids can offer an alternative pathway for incorporating saturated cyclic amine cores into polycyclic products.^{12,13} Gratifyingly, condensations of cyanomethylbenzaldehyde (**1a**) with either L-proline or ($\pm$)-pipecolic acid provided the corresponding products **3** and **4** in moderate yields (Scheme 4).

Regarding the diastereoselectivity of the redox-annulations, we suspected that products are not configurationally stable under the reaction conditions as interconversion of the two diastereomers could potentially occur via a retro-Mannich/Mannich pathway. In this case, the dr of the product would represent the thermodynamic equilibrium ratio of the two diastereomers, rather than reflecting the relative reaction barriers for their formation. Indeed, as illustrated by the experiments summarized in Scheme 5, both diastereomers of **2n** converge to the same diastereomeric mixture when exposed individually to the reaction conditions.

In the course of our studies, we “rediscovered” an interesting transformation that enables the facile conversion of the β -aminonitrile annulation products into β -aminoalcohols.¹⁴

Specifically, upon attempted reduction of the nitrile functionality of **2a** (used as a 4:1 mixture of diastereomers) with lithium aluminum hydride, β -aminoalcohol **5** was obtained diastereoselectively in 62% yield (Scheme 6).¹⁵ An analogous reaction with the pure major diastereomer of **2a** provided nearly identical results (not shown), indicating a common intermediate. These observations are consistent with the previously proposed mechanism of this transformation.¹⁴

In summary, we have achieved redox-annulations of THIQ and related amines with *ortho*-cyanomethylbenzaldehydes, in addition to a decarboxylative variant of this process. The resulting products can be readily converted to polycyclic β -aminoalcohols possessing a tetrahydroprotoberberine core.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Financial support from the NIH–NIGMS (Grant R01GM101389) is gratefully acknowledged. We thank Dr. Tom Emge (Rutgers University) for X-ray crystallographic analysis.

REFERENCES

- (1). Selected recent reviews on amine C–H functionalization, including redox-neutral approaches: Direct sp^3 C–H bond activation adjacent to nitrogen in heterocycles. Campos KR Chem. Soc. Rev 2007, 36, 1069–1084; [PubMed: 17576475] Functionalization of Organic Molecules by Transition-Metal-Catalyzed C(sp^3)-H Activation. Jazzar; Hitce; Renaudat A; Sofack-Kreutzer J; Baudoin O Chem. Eur. J 2010, 16, 2654–2672; [PubMed: 20143359] Catalytic Dehydrogenative Cross-Coupling: Forming Carbon-Carbon Bonds by Oxidizing Two Carbon-Hydrogen Bonds. Yeung CS; Dong VM Chem. Rev 2011, 111, 1215–1292; [PubMed: 21391561] Direct α -Functionalization of Saturated Cyclic Amines. Mitchell EA; Peschiulli A; Lefevre N; Meerpoel L; Maes BUW Chem. Eur. J 2012, 18, 10092–10142; [PubMed: 22829434] Oxidative Coupling of Tertiary Amines: Scope, Mechanism and Challenges. Jones KM; Klussmann M Synlett 2012, 23, 159–162; The Redox-Neutral Approach to C–H Functionalization. Peng; Maulide Chem. Eur. J 2013, 19, 13274–13287; [PubMed: 24027042] The Cross-Dehydrogenative Coupling of C sp^3 -H Bonds: A Versatile Strategy for C–C Bond Formations. Girard SA; Knauber T; Li C-J Angew. Chem. Int. Ed 2014, 53, 74–100; C–H Bond Functionalization through Intramolecular Hydride Transfer. Haibach MC; Seidel D Angew. Chem. Int. Ed 2014, 53, 5010–5036; Advancement in Cascade [1,n]-Hydrogen Transfer/Cyclization: A Method for Direct Functionalization of Inactive C(sp^3)-H Bonds. Wang L; Xiao J Adv. Synth. Catal 2014, 356, 1137–1171; Synthesis of Saturated N-Heterocycles. Vo C-VT; Bode JW J. Org. Chem 2014, 79, 2809–2815; [PubMed: 24617516] The redox-A3 reaction. Seidel D Org. Chem. Front 2014, 1, 426–429; [PubMed: 24955245] 1) Catalytic asymmetric α -C(sp^3)-H functionalization of amines. Qin Y; Lv J; Luo S Tetrahedron Lett 2014, 55, 551–558; The Azomethine Ylide Route to Amine C–H Functionalization: Redox-Versions of Classic Reactions and a Pathway to New Transformations. Seidel D Acc. Chem. Res 2015, 48, 317–328; [PubMed: 25560649] Amine Functionalization via Oxidative Photoredox Catalysis: Methodology Development and Complex Molecule Synthesis. Beatty JW; Stephenson CRJ Acc. Chem. Res 2015, 48, 1474–1484; [PubMed: 25951291] Classical-Reaction-Driven Stereo- and Regioselective C(sp^3)-H Functionalization of Aliphatic Amines. Mahato S; Jana CK Chem. Rec 2016, 16, 1477–1488; [PubMed: 27185195] Organocatalysis in Inert C–H Bond Functionalization. Qin Y; Zhu L; Luo S Chem. Rev 2017, 117, 9433–9520; [PubMed: 28697602] Recent Advances in the Enantioselective Oxidative α -C–H Functionalization of Amines. Cheng M-X; Yang S-D Synlett 2017, 28, 159–174; Transition metal-catalyzed α -alkylation of amines by

C(sp³)–H bond activation. Gonnard L; Guérinot A; Cossy J *Tetrahedron* 2019, 75, 145–163; Construction of N-Heterocycles through Cyclization of Tertiary Amines. Liu S; Zhao Z; Wang Y *Chem. Eur. J* 2019, 25, 2423–2441; [PubMed: 30357981] Transition Metal-Catalyzed Directed C(sp³)–H Functionalization of Saturated Heterocycles. Antermite D; Bull JA *Synthesis* 2019, 51, 3171–3204.

- (2). Recent examples of mechanistically distinct amine C–H bond functionalization reactions: Palladium-Catalyzed Enantioselective C–H Activation of Aliphatic Amines Using Chiral Anionic BINOL-Phosphoric Acid Ligands. Smalley AP; Cuthbertson JD; Gaunt MJ J. Am. Chem. Soc 2017, 139, 1412–1415; [PubMed: 28064488] Synthesis of Ring-Fused 1-Benzazepines via [1,5]-Hydride Shift/7-Endo Cyclization Sequences. Suh CW; Kwon SJ; Kim DY *Org. Lett* 2017, 19, 1334–1337; [PubMed: 28234485] Direct Intermolecular C–H Functionalization Triggered by 1,5-Hydride Shift: Access to N-Arylprolinamides via Ugi-Type Reaction. Zhen L; Wang J; Xu Q-L; Sun H; Wen X; Wang G *Org. Lett* 2017, 19, 1566–1569; [PubMed: 28290693] Synthesis of Spirooxindoles via the tert-Amino Effect. Ramakumar K; Maji T; Partridge JJ; Tunge JA *Org. Lett* 2017, 19, 4014–4017; [PubMed: 28737400] Construction of the tetrahydroquinoline spiro skeleton via cascade [1,5]-hydride transfer-involved C(sp³)–H functionalization “on water”. Zhu S; Chen C; Xiao M; Yu L; Wang L; Xiao J *Green Chem* 2017, 19, 5653–5658; Organocatalytic C(sp³)–H Functionalization via Carbocation-Initiated Cascade [1,5]-Hydride Transfer/Cyclization: Synthesis of Dihydrodibenzo[b,e]azepines. Li S-S; Zhou L; Wang L; Zhao H; Yu L; Xiao J *Org. Lett* 2018, 20, 138–141; [PubMed: 29239184] Direct α -C–H bond functionalization of unprotected cyclic amines. Chen W; Ma L; Paul A; Seidel D *Nat. Chem* 2018, 10, 165; [PubMed: 29359746] Intramolecular hydride transfer onto arynes: redox-neutral and transition metal-free C(sp³)–H functionalization of amines. Idiris FIM; Majeste CE; Craven GB; Jones CR *Chem. Sci* 2018, 9, 2873–2878; [PubMed: 29732071] Redox-triggered cascade dearomative cyclizations enabled by hexafluoroisopropanol. Li S-S; Lv X; Ren D; Shao C-L; Liu Q; Xiao J *Chem. Sci* 2018, 9, 8253–8259; [PubMed: 30542574] Second-Generation Palladium Catalyst System for Transannular C–H Functionalization of Azabicycloalkanes. Cabrera PJ; Lee M; Sanford MS J. Am. Chem. Soc 2018, 140, 5599–5606; [PubMed: 29652497] Chiral Magnesium Bisphosphate-Catalyzed Asymmetric Double C(sp³)–H Bond Functionalization Based on Sequential Hydride Shift/Cyclization Process. Mori K; Isogai R; Kamei Y; Yamanaka M; Akiyama T J. Am. Chem. Soc 2018, 140, 6203–6207; [PubMed: 29741877] C–H Functionalization of Amines via Alkene-Derived Nucleophiles through Cooperative Action of Chiral and Achiral Lewis Acid Catalysts: Applications in Enantioselective Synthesis. Shang M; Chan JZ; Cao M; Chang Y; Wang Q; Cook B; Torker S; Wasa M J. Am. Chem. Soc 2018, 140, 10593–10601; [PubMed: 30045617] Electrochemical Aminoxyl-Mediated α -Cyanation of Secondary Piperidines for Pharmaceutical Building Block Diversification. Lennox AJJ; Goes SL; Webster MP; Koolman HF; Djuric SW; Stahl SS J. Am. Chem. Soc 2018, 140, 11227–11231; [PubMed: 30141925] Borane-Catalyzed Synthesis of Quinolines Bearing Tetrasubstituted Stereocenters by Hydride Abstraction-Induced Electrocyclization. Maier AFG; Tussing S; Zhu H; Wicker G; Tzvetkova P; Flörke U; Daniliuc CG; Grimme S; Paradies J *Chem. Eur. J* 2018, 24, 16287–16291; [PubMed: 30230618] Expedient synthesis of multisubstituted indoles via multiple hydrogen transfers. Yoshida T; Mori K *Chem. Commun* 2018, 54, 12686–12689; B(C₆F₅)₃-Catalyzed C–H Alkylation of N-Alkylamines Using Silicon Enolates without External Oxidant. Chan JZ; Chang Y; Wasa M *Org. Lett* 2019, 21, 984–988; [PubMed: 30693779] Redox-Neutral β -C(sp³)–H Functionalization of Cyclic Amines via Intermolecular Hydride Transfer. Zhou L; Shen Y-B; An X-D; Li X-J; Li S-S; Liu Q; Xiao J *Org. Lett* 2019, 21, 8543–8547; [PubMed: 31633932] Primary α -tertiary amine synthesis via α -C–H functionalization. Vasu D; Fuentes de Arriba AL; Leitch JA; de Gombert A; Dixon DJ *Chem. Sci* 2019, 10, 3401–3407; [PubMed: 30996928] Deoxygenative Insertion of Carbonyl Carbon into a C(sp³)–H Bond: Synthesis of Indolines and Indoles. Asako S; Ishihara S; Hirata K; Takai K J. Am. Chem. Soc 2019, 141, 9832–9836; [PubMed: 31184481] A General Acid-Mediated Hydroaminomethylation of Unactivated Alkenes and Alkynes. Kaiser D; Tona V; Gonçalves CR; Shaaban S; Oppedisano A; Maulide N *Angew. Chem. Int. Ed* 2019, 58, 14639–14643.
- (3). a) α -Amination of Nitrogen Heterocycles: Ring-Fused Aminals. Zhang C; De CK; Mal R; Seidel D J. Am. Chem. Soc 2008, 130, 416–417; [PubMed: 18081292] b) A Cascade Reaction with Iminium Ion Isomerization as the Key Step Leading to Tetrahydropyrimido[4,5-d]pyrimidines. Zheng L; Yang F; Dang Q; Bai X *Org. Lett* 2008, 10, 889–892; [PubMed: 18081292]

18260668] c)Metal-Free α -Amination of Secondary Amines: Computational and Experimental Evidence for Azaquinone Methide and Azomethine Ylide Intermediates.Dieckmann A; Richers MT; Platonova AY; Zhang C; Seidel D; Houk KN J. Org. Chem 2013, 78, 4132–4144; [PubMed: 23517448] d)Facile Access to Ring-Fused Aminals via Direct α -Amination of Secondary Amines with o-Aminobenzaldehydes: Synthesis of Vasicine, Deoxyvasicine, Deoxyvasicinone, Mackinazolinone, and Ruteacarpine.Richers MT; Deb I; Platonova AY; Zhang C; Seidel D Synthesis 2013, 45, 1730–1748.

- (4). a)Redox-Neutral α -Oxygenation of Amines: Reaction Development and Elucidation of the Mechanism.Richers MT; Breugst M; Platonova AY; Ullrich A; Dieckmann A; Houk KN; Seidel D J. Am. Chem. Soc 2014, 136, 6123–6135; [PubMed: 24689802] b)Redox-Neutral α -Sulfonylation of Secondary Amines: Ring-Fused N,S-Acetals.Jarvis CL; Richers MT; Breugst M; Houk KN; Seidel D Org. Lett 2014, 16, 3556–3559; [PubMed: 24927364] c)Divergent reaction: metal & oxidant free direct C-H aryloxylation and hydride free formal reductive N-benylation of N-heterocycles.Mahato S; Haque MA; Dwari S; Jana CK RSC Adv 2014, 4, 46214–46217.
- (5). Intramolecular Redox-Mannich Reactions: Facile Access to the Tetrahydropyprotoberberine Core.Ma L; Seidel D Chem. Eur. J 2015, 21, 12908–12913. [PubMed: 26220197]
- (6). a)Lewis Acid-Catalyzed C(sp³)-C(sp³) Bond Forming Cyclization Reactions for Synthesis of Tetrahydropyprotoberberine Derivatives.Li J; Qin C; Yu Y; Fan H; Fu Y; Li H; Wang W Adv. Synth. Catal 2017, 359, 2191–2195;b)Asymmetric synthesis of isoquinolinonaphthyridines catalyzed by a chiral Bronsted acid.Li J; Fu Y; Qin C; Yu Y; Li H; Wang W Org. Biomol. Chem 2017, 15, 6474–6477; [PubMed: 28737793] c)Acetic Acid Promoted Redox Annulations with Dual C–H Functionalization.Zhu Z; Seidel D Org. Lett 2017, 19, 2841–2844. [PubMed: 28510444]
- (7). Redox-Annulations of Cyclic Amines with Electron-Deficient o-Tolualdehydes.Paul A; Adili A; Seidel D Org. Lett 2019, 21, 1845–1848. [PubMed: 30840479]
- (8). Additional examples of amine redox-annulations:Azomethine ylide annulations: facile access to polycyclic ring systems.Zhang C; Das D; Seidel D Chem. Sci 2011, 2, 233–236;Asymmetric Redox-Annulation of Cyclic Amines.Kang Y; Chen W; Breugst M; Seidel D J. Org. Chem 2015, 80, 9628–9640; [PubMed: 26348653] Redox-Annulation of Cyclic Amines and β -Ketoaldehydes.Chen W; Seidel D Org. Lett 2016, 18, 1024–1027; [PubMed: 26895555] Synthesis of Polycyclic Imidazolidinones via Amine Redox-Annulation.Zhu Z; Lv X; Anesini JE; Seidel D Org. Lett 2017, 19, 6424–6427; [PubMed: 29144764] Redox-Annulations of Cyclic Amines with 2-(2-Oxoethyl)malonates.Zhu Z; Chandak HS; Seidel D Org. Lett 2018, 20, 4090–4093; [PubMed: 29939750] Synthesis of 1,2-Fused Bicyclic Imidazolidin-4-ones by Redox-Neutral Cyclization Reaction of Cyclic Amines and α -Ketoamides.Liu Y; Wu J; Jin Z; Jiang H Synlett 2018, 29, 1061–1064.
- (9). For detailed discussions on the mechanisms of these transformations, see references 1m, 3c, 4a, 4b, 8b, and the following reports:A Computational Reinvestigation of the Formation of N-Alkylpyrroles via Intermolecular Redox Amination.Xue X; Yu A; Cai Y; Cheng J-P Org. Lett 2011, 13, 6054–6057; [PubMed: 22014326] Redox-Neutral Aromatization of Cyclic Amines: Mechanistic Insights and Harnessing of Reactive Intermediates for Amine α - and β -C–H Functionalization.Ma L; Paul A; Breugst M; Seidel D Chem. Eur. J 2016, 22, 18179–18189. [PubMed: 27712000]
- (10). Examples of redox-neutral α -C–H bond annulations of secondary amines that likely involve a pericyclic step:X=Y-ZH systems as potential 1,3-dipoles. Part 26. 1,5-electrocyclisation and tandem 1,5-electrocyclisationAldol type condensation processes in imines.Grigg R; Nimal Gunaratne HQ; Henderson D; Sridharan V Tetrahedron 1990, 46, 1599–1610;A one pot synthesis of 5,7-diphenyl-2,3-dihydro-1H-pyrrolizine.Soeder RW; Bowers K; Pegram LD; Cartaya-Marin CP Synth. Commun 1992, 22, 2737–2740;X=Y-ZH Systems as potential 1,3-dipoles. Part 38. 1,5-Electrocyclisation of vinyl- and iminyl-azomethine ylides. 2-Azaindolizines and pyrrolo-dihydro-isoquinolines.Grigg R; Kennewell P; Savic V; Sridharan V Tetrahedron 1992, 48, 10423–10430;Retro-Claisen condensation versus pyrrole formation in reactions of amines and 1,3-diketones.Deb I; Seidel D Tetrahedron Lett 2010, 51, 2945–2947;C-H functionalization of cyclic amines: redox-annulations with α,β -unsaturated carbonyl compounds.Kang Y; Richers MT; Sawicki CH; Seidel D Chem. Commun 2015, 51, 10648–10651;Redox-Triggered α -C–H Functionalization of Pyrrolidines: Synthesis of Unsymmetrically 2,5-Disubstituted

- Pyrrolidines. Cheng Y-F; Rong H-J; Yi C-B; Yao J-J; Qu J. *Org. Lett* 2015, 17, 4758–4761; [PubMed: 26378343] Base-Promoted Intermolecular Cyclization of Substituted 3-Aryl(Heteroaryl)-3-chloroacrylaldehydes and Tetrahydroisoquinolines: An Approach to Access Pyrrolo[2,1-a]isoquinolines. Yang Z; Lu N; Wei Z; Cao J; Liang D; Duan H; Lin Y J. *Org. Chem* 2016, 81, 11950–11955; [PubMed: 27802591] Synthesis of γ -Lactams by Mild, o-Benzoquinone-Induced Oxidation of Pyrrolidines Containing Oxidation-Sensitive Functional Groups. Rong H-J; Cheng Y-F; Liu F-F; Ren S-J; Qu J J. *Org. Chem* 2017, 82, 532–540; [PubMed: 27976902] Metal-Free Sequential C(sp²)-H/OH and C(sp³)-H Aminations of Nitrosoarenes and N-Heterocycles to Ring-Fused Imidazoles. Purkait A; Roy SK; Srivastava HK; Jana CK. *Org. Lett* 2017, 19, 2540–2543. [PubMed: 28485602]
- (11). a) Asymmetric synthesis of isoquinoline alkaloids. Chrzanowska M; Rozwadowska MD. *Chem. Rev* 2004, 104, 3341–3370; [PubMed: 15250744] b) Quaternary protoberberine alkaloids. Grycova L; Dostal J; Marek R. *Phytochemistry* 2007, 68, 150–175; [PubMed: 17109902] c) Therapeutic Potential of Nucleic Acid-Binding Isoquinoline Alkaloids: Binding Aspects and Implications for Drug Design. Bhadra K; Kumar GS. *Med. Res. Rev* 2011, 31, 821–862; [PubMed: 20077560] d) Evolution of two routes for asymmetric total synthesis of tetrahydroprotoberberine alkaloids. Yu J; Zhang Z; Zhou S; Zhang W; Tong R. *Org. Chem. Front* 2018, 5, 242–246.
- (12). a) A novel sterically mediated transformation of proline. Cohen N; Blount JF; Lopresti RJ; Trullinger DP. *J. Org. Chem* 1979, 44, 4005–4007; b) Benzoic Acid Catalyzed Annulations of α -Amino Acids and Aromatic Aldehydes Containing an ortho-Michael Acceptor: Access to 2,5-Dihydro-1H-benzo[c]azepines and 10,11-Dihydro-5H-benzo[e]pyrrolo[1,2-a]azepines. Tang M; Tong L; Ju L; Zhai W; Hu Y; Yu X. *Org. Lett* 2015, 17, 5180–5183; [PubMed: 26488671] c) Decarboxylative Annulation of α -Amino Acids with γ -Nitroaldehydes. Kang Y; Seidel D. *Org. Lett* 2016, 18, 4277–4279; [PubMed: 27509449] d) Novel synthesis of tetrahydro-1H-pyrrolo[1,2-a]imidazol-2-ones via decarboxylative cyclization reaction of α -amino acids and α -ketoamides. Wu J.-s.; Jiang H.-j.; Yang J.-g.; Jin Z.-n.; Chen D.-b. *Tetrahedron Lett* 2017, 58, 546–551; e) Decarboxylative Annulation of α -Amino Acids with β -Ketoaldehydes. Paul A; Thimmegowda NR; Galani Cruz T; Seidel D. *Org. Lett* 2018, 20, 602–604. [PubMed: 29328663] See also references 3a, 3b, 3d, 6c, 8a, 8e.
- (13). Selected reviews on decarboxylative coupling reactions not limited to amino acids: Decarboxylative coupling reactions: a modern strategy for C-C bond formation. Rodriguez N; Goossen LJ. *Chem. Soc. Rev* 2011, 40, 5030–5048; [PubMed: 21792454] Visible-Light-Induced Decarboxylative Functionalization of Carboxylic Acids and Their Derivatives. Xuan J; Zhang Z-G; Xiao W-J. *Angew. Chem. Int. Ed* 2015, 54, 15632–15641; Decarboxylation as the Key Step in C-C Bond-Forming Reactions. Patra T; Maiti D. *Chem. Eur. J* 2017, 23, 7382–7401; [PubMed: 27859719] Metal-Catalyzed Decarboxylative C-H Functionalization. Wei Y; Hu P; Zhang M; Su W. *Chem. Rev* 2017, 117, 8864–8907; [PubMed: 28266216] Recent Advances on Diverse Decarboxylative Reactions of Amino Acids. Rahman M; Mukherjee A; Kovalev IS; Kopchuk DS; Zyryanov GV; Tsurkan MV; Majee A; Ranu BC; Charushin VN; Chupakhin ON; Santra S. *Adv. Synth. Catal* 2019, 361, 2161–2214.
- (14). Reactions of some carbanions generated with lithium aluminium hydride. Collins D; Hobbs J. *Aust. J. Chem* 1974, 27, 1731–1741.
- (15). The expected reduction product was observed in trace amounts.

Redox-annulation of amines with activated *ortho*-substituted benzaldehydes: **Redox-annulation with 2-alkylquinoline-3-carbaldehydes:** **Redox-annulation with electron-deficient *ortho*-tolualdehydes:** **Redox-annulation with moderately activated *ortho*-tolualdehydes (this work):**

Scheme 1.
Selected Redox-Annulations of Amines

Scheme 2. Scope of the aldehyde^a

^a Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields.^b
 Performed on a 1 mmol scale.

Scheme 3. Scope of the amine^a

^a Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields.^b Two equiv of the amine were used.

Scheme 4. Decarboxylative annulations^a^a Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields.

Scheme 5.

Equilibration of product diastereomers

^a AcOH (20 equiv), 1,2-dichloroethane, reflux, 4 h.

Scheme 6.
Unexpected product modification

Table 1.

Reaction Development^a

entry	THIQ equiv	acid (equiv)	solvent	dr	yield (%)
1	1.3	PhCOOH (1.3)	C ₂ H ₄ Cl ₂	1:1	81
2	1.3	AcOH (1.3)	C ₂ H ₄ Cl ₂	2:1	94
3	1.3	AcOH (5)	C ₂ H ₄ Cl ₂	2.5:1	96
4	1.3	AcOH (10)	C ₂ H ₄ Cl ₂	3:1	94
5	1.3	AcOH (20)	C ₂ H ₄ Cl ₂	4:1	92
6	1.3	AcOH (20)	PhMe	3:1	81
7	1.3	AcOH (87.5) ^b	PhMe	2:1	64
8 ^c	1.3	AcOH (20)	C ₂ H ₄ Cl ₂	4:1	91
9	2	AcOH (20)	C ₂ H ₄ Cl ₂	4:1	93
10	1	AcOH (20)	C ₂ H ₄ Cl ₂	3:1	79

^aReactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields.^bCorresponds to a 1:1 mixture of AcOH and PhMe.^cReaction was performed in the presence of 4 Å MS.